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August 23, 2018

Monique Vela
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P.O. Box 4010
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Re: Proposed Adoption of New Section Under Article 7: No Significant Risk Levels
Section 25704: Exposures to Listed Chemicals in Coffee Posing No Significant Risk

Dear Ms. Vela:

I have read OEHHA's Initial Statement of Reasons (ISOR) for its proposed regulation that would declare all listed heat-formed carcinogens in coffee to present no significant risk of cancer, and wish to comment regarding the lack of a scientific basis for this proposed regulation.

I am a Professor of Toxicology in the School of Public Health at the University of California at Berkeley where I hold the Kenneth Howard and Marjorie Witherspoon Kaiser Endowed Chair in Cancer Epidemiology. My expertise and background is in molecular epidemiology, toxicology, and genomics, aimed at finding the causes of chronic disease. One area of my research has focused on chemically-induced leukemia, including the causes of childhood leukemia. One of my papers regarding the identification of human carcinogens using the established mechanisms of cancer is cited in the Initial Statement of Reasons.[1] My curriculum vitae which lists my relevant publications is submitted herewith.

These comments reflect my own opinions rather than those of my colleagues in the School of Public Health at UC Berkeley or of the University. I also wish to disclose that I have provided expert consultation and testimony at the request of the Council for Education and Research on Toxics in the Proposition 65 case against the coffee industry referenced in the ISOR and that I am currently funded to perform research on endocrine disruptors and reproductive toxicants by OEHHA under contract 17-E0023.

I wish to make five points regarding OEHHA's lack of a scientific basis for the proposed regulation:

1) OEHHA has misinterpreted IARC's conclusion on coffee.

2) OEHHA claims that coffee protects against certain cancers, basing its conclusions on IARC. However, science has advanced since the IARC evaluation and the use of Mendelian randomization has shown that coffee is not protective against chronic diseases, including cancer.

3) OEHHA suggests that coffee protects against certain cancers by means of an antioxidant mechanism. This is speculative and probably incorrect, because there is no scientific evidence that antioxidants in coffee are protective of human health, including cancer.

4) There is quite compelling evidence that coffee intake by the mother during pregnancy increases the rate of childhood leukemia.

5) Coffee contains caffeine, which is clearly a developmental toxicant. Students in my class this past spring did an analysis that showed the safe level of intake for caffeine was less than 50 mg for a pregnant woman in order to prevent retardation of growth of the fetus. This is less than one cup of coffee per day.

Based on these and other considerations, I would recommend that OEHHA withdraw its proposed regulation because the scientific rationale for the regulation is seriously flawed.

1. OEHHA Has Misinterpreted the IARC's Conclusion on Coffee

I was the U.S. representative on the Scientific Council of IARC from 2012-16 and have served on IARC Working Groups for a number of chemicals that it has evaluated for human carcinogenicity. I am therefore very familiar with the IARC system for the classification of carcinogens and the scientific standards it follows in its evaluations.

In its recently published monograph, IARC concluded that coffee is not classifiable as to its carcinogenicity to humans.[2] IARC reached this conclusion because of the large amount of conflicting evidence and the nature and quality of the relevant published studies.

The Preamble[3] to the IARC Monographs explains IARC's Group 3 classification as follows: "**An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety.** It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations." Although the IARC's classification of coffee "is not a determination of non-carcinogenicity or overall safety," OEHHA appears to interpret IARC's conclusion as meaning that coffee does not cause human cancer and is safe. This is incorrect.

Had IARC concluded that consumption of coffee does not cause human cancer, IARC would have classified coffee in Group 4 rather than Group 3. IARC classifies an agent in Group 4 when it concludes that the agent is ***probably not carcinogenic to humans.*** According to the Preamble: "This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carincogenicity* in experimental animals, consistently and strongly supported by a broad range of

mechanistic and other relevant data, may be classified in this group."

Since IARC concluded that coffee is *not classifiable* as to its carcinogenicity to humans (Group 3) rather than concluding that coffee s *probably not carcinogenic* to humans, it is inappropriate for OEHHA to conclude, based on IARC, that coffee does not cause human cancer. It is especially inappropriate for OEHHA to have concluded, based on IARC, that consumption of coffee prevents human cancer or protects against the development of human cancer. In my view, this is a gross misinterpretation of IARC's conclusion regarding the carcinogenicity of coffee to humans.

2. Mendelian Randomization Studies Show that Coffee Does Not Prevent Cancer

The IARC Working Group on Coffee met in May 2016 to evaluate the published literature available relevant to the carcinogenicity of coffee that was then available. At that time a large number of epidemiological studies had been published. However, all the studies were observational studies, which are generally considered inadequate to determine causality for dietary constituents.[4] Although the IARC Monograph on Coffee was published on June 13, 2018, the Monograph does not include any literature published since May of 2016, because the Working Group's evaluation of the carcinogenicity of coffee to humans was based on the literature available at that time. However, since IARC's evaluation in May of 2016, several powerful and important Mendelian randomization studies regarding consumption of coffee and chronic diseases, including cancer, have been published.

As explained in a recent review, "Mendelian randomization (MR) uses genetic variants to proxy modifiable exposures to generate more reliable estimates of the causal effects of these exposures on diseases and their outcomes. . . . Analyses using genetic variants as instruments to examine associations with outcomes have a number of advantages: i) effect estimates should be less prone to the confounding that typically distorts conventional observational associations, ii) because germline genetic variants are fixed at conception, they cannot be modified by subsequent factors, thus overcoming possible issues of reverse causation, and iii) measurement error in genetic studies is often low as modern genotyping technologies provide relatively precise measurement of genetic variants, unlike the substantial (and at times differential) exposure measurement error which can accompany observations studies (e.g., due to self-report)."[5] Thus, whereas observational studies are inadequate to evaluate causality of dietary factors, Mendelian randomization studies can do so.

Since IARC's evaluation in 2016, Mendelian randomization studies regarding coffee have been published to determine whether inverse associations reported in observational epidemiologic studies regarding coffee consumption and chronic diseases are causal or artefactual. In the last few years, Mendelian randomization studies have been published regarding coffee and Type 2 diabetes,[6] Alzheimer's disease,[7] cardiovascular disease,[8] prostate cancer,[9] and epithelial ovarian cancer.[10] These studies have not reported inverse associations for these diseases and indicate that the inverse associations reported in observational studies regarding coffee are not causal, but are most likely due to confounding and reverse causation.

Although observational studies have consistently reported inverse associations between coffee consumption and Alzheimer's disease,[11] a well-conducted Mendelian randomization study reported that genetically predicted higher consumption of coffee significantly increased the risk of Alzheimber's disease (OR 1.26, 95% CI 1.05 - 1.51, $p = 0.01$). In fact, of all 24 potentially modifiable risk factors investigated, only genetically predicted higher coffee consumption significantly increased the risk of Alzheimer's disease.[12] Similarly, although some observational studies have reported inverse associations between coffee consumption and prostate cancer, a Mendelian randomization study of genetically predicted coffee consumption did not confirm the inverse association, but instead reported a small, but significantly increased risk of nonlocalized prostate cancer compared to localized stage disease (OR 1.03, 95% CI 1.01 - 1.06).[13]

Thus, Mendelian randomization studies published to date do not support a protective effect of coffee consumption on chronic disease, including cancer. OEHHA's conclusion that consumption of coffee prevents the development of human cancer is therefore not supported and is, in fact, refuted by the Mendelian randomization studies regarding coffee published in the last few years.

3. The Proposed Antioxidant Mechanism for Cancer Prevention is Speculative and Probably Wrong

In the Initial Statement of Reasons, OEHHA suggests that coffee protects against certain cancers by means of an antioxidant mechanism. This is speculative and probably incorrect, because there is no solid scientific evidence that antioxidants in coffee are protective of human health. While many observational studies have reported decreased mortality and chronic diseases, including cancer in association with antioxidant intake, randomized controlled trials have not confirmed a beneficial effect of antioxidant intake on human health, but have rather shown that increased antioxidant intake increases mortality as well as some chronic diseases, including certain cancers. Indeed, over the last fifteen years, multiple randomized controlled trials and meta-analyses of trials have shown that antioxidants have no beneficial effect and some antioxidants have been shown to cause harm.

In 2007 a meta-analysis of 47 low-bias trials involving 180,938 participants showed that compared with the control group, the antioxidant supplement group exhibited a mortality rate that was significantly increased (RR 1.05, 95% CI 1.02 - 1.08). In low-bias risk trials, after excluding selenium trials, significantly increased mortality was observed for beta carotene (RR 1.07, 95% CI 1.02 - 1.11), vitamin A (RR 1.16, 95% CI 1.10 - 1.24) and vitamin E (RR 1.04, 95% CI 1.01-1.07).[14]

A Cochrane systematic review published in 2012 included 78 randomized clinical trials. In total, 296,707 participants were randomized to antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus placebo or no intervention. Twenty-six trials included 215,900 healthy participants. Fifty-two trials included 80,807 participants with various diseases in a stable phase (including gastrointestinal, cardiovascular, neurological, ocular, dermatological, rheumatoid, renal, endocrinological, or unspecified diseases). A total of 21,484 of 183,749 participants (11.7%) randomized to antioxidant supplements and 11,479 of

112,958 participants (10.2%) randomized to placebo or no intervention died. When all of the trials were combined, antioxidant use slightly increased mortality, i.e., the patients consuming the antioxidants were 1.03 times as likely to die as were the controls. When the trials with low risks of bias were considered separately, the increased mortality was even more pronounced (1.04 times as likely to die as were the controls). The increased risk of mortality was associated with beta-carotene and possibly vitamin E and vitamin A. The authors of this concluded that the current evidence does not support the use of antioxidant supplements in the general population or in patients with various diseases.[15]

A meta-analysis of 12 clinical trials published in 2008 undertook to estimate the association between antioxidant use and primary cancer incidence and mortality, and to evaluate these effects across specific antioxidant compounds, target organs, and participant subgroups. Nine trials of high methodological quality were identified, comprising a total subject population of 104,196. Antioxidant supplementation did not significantly reduce total cancer incidence (RR 0.99, 95% CI 0.94 - 1.04) or mortality (RR 1.03, 95% CI 0.92 - 1.15) or any site-specific cancer incidence. Beta-carotene supplementation was associated with increased cancer incidence among smokers (RR 1.10, 95% CI 1.03 - 1.10), with a trend toward increased cancer mortality (RR 1.16, 95% CI 0.98 - 1.37).[16]

A meta-analysis of randomized controlled trials of the effect of antioxidant supplements on cancer was published by Korean researchers in 2010. They identified 31 articles on 22 randomized controlled trials, which included 161,045 subjects, 88,610 in antioxidant supplement groups and 72,435 in placebo or no-intervention groups. In a fixed-effects meta-analysis of all 22 trials, antioxidant supplements were found to have no preventive effect on cancer (RR 0.99, 95% CI 0.96 - 1.03). Similar findings were observed in 12 studies on primary prevention trials (RR 1.00, 95% CI 0.97 - 1.04) and in nine studies on secondary prevention trials (RR 0.97, 95% CI 0.83 - 1.13). Subgroup analyses revealed no preventive effect on cancer according to type of antioxidant, type of cancer, or the methodological quality of the studies. However, the use of antioxidant supplements significantly increased the risk of bladder cancer (RR 1.52, 95% CI 1.06 - 2.17) in a subgroup meta-analysis of four trials. The researchers concluded that their meta-analysis of randomized controlled trials indicated there is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer, but that use of antioxidants may cause some cancers.[17]

A meta-analysis of 21 randomized controlled trials, published in 2013, found no significant effect on mortality due to cancer (RR 0.96, 95% CI 0.88 - 1.04).[18]

A meta-analysis of primary prevention trials, was undertaken by German researchers in 2017 to assess the efficacy of dietary supplements in the primary prevention of cause-specific death, cardiovascular disease, and cancer. A total of 49 trials including 287,304 participants met the inclusion criteria. Overall, the meta-analysis revealed no significant reduction in cancer with dietary supplements, however vitamin A was shown to increase cancer risk (RR 1.16, 95% CI 1.00 - 1.35).[19]

Meta-analyses of randomized controlled trials have been undertaken to determine the effect of vitamin and antioxidant supplementation in the prevention of particular cancers. Such

meta-analyses have found no significant reduction of risk for bladder cancer,[20] breast cancer,[21] colorectal cancer and adenomas,[22] esophageal cancer,[23] gastrointestinal cancers,[24] prostate cancer,[25] and skin cancer.[26] While these studies showed no evidence of cancer risk reduction, some of them reported increased risks of cancer with particular antioxidant vitamins. Thus, in meta-analyses beta-carotene was reported to significantly increase the risk of bladder cancer [27] and gastrotinestinal cancer,[28] while vitamin E and vitamin E plus beta-carotene were reported to significantly increase the risk of colorectal cancer[29] and gastrointestinal cancer.[30] Thus, if antioxidants have any effect on cancer, they probably increase cancer incidence and mortality rather than preventing the occurrence of cancer. OEHHA appears to base its conclusion that antioxidants prevent cancer on the IARC Monograph. However, while the Monograph discusses studies of antioxidants in coffee and cancer, those studies show conflicting results and IARC does not conclude that antioxidants in coffee prevent cancer.

4. There is Compelling Evidence that Maternal Coffee Intake Increases the Risk of Childhood Leukemia

IARC identified "[s]even case-control studies reporting results of the association between maternal coffee consumption during pregnancy and risk of childhood leukaemia in the offspring."[31] "The Working Group considered that the earliest two studies were of limited quality due to low participation fractions and uninformative categories."[32] Of the five studies that IARC considered to be of sufficient quality for analysis, all reported significantly increased risks of childhood leukemia in association with maternal consumption of coffee during pregnancy.[33]

IARC also noted that "three meta-analyses of the association between maternal coffee consumption and childhood leukaemia have been conducted, and all reported elevated risks with higher levels of maternal coffee intake."[34] The meta-analyses reported statistically significant increased risks of both types of childhood leukemia. IARC noted that the most recent meta-analysis that "included all studies published to date," "high maternal coffee intake during pregnancy was positively associated with AL [acute leukemia] overall, ALL and AML, with summary odds ratios (95% CI) of 1.57 (1.16 - 2.11), 1.42 (1.22 - 1.68), and 1.81 (0.93 - 3.53), respectively."[35]

Since IARC reviewed the studies regarding maternal consumption of coffee during pregnancy and childhood leukemia in 2016, an important study regarding the association has been published. In 2018 researchers from the Childhood Leukemia International Consortium investigated the effects of maternal consumption of coffee and tea during pregnancy on childhood acute lymphoblastic leukemia by pooling data from eight case-control studies. Data on maternal coffee intake were available for 2,552 cases and 4,876 controls. Data on genetic variants in *NAT2, CYP1A1,* and *NQO1* were also available in a subset. Pooled odds ratios and 95 confidence intervals were estimated using unconditional logistic regression and linear trends across categories were assessed. They found evidence of a positive exposure-response; the pooled odds ratio for consumption of coffee of more than 2 cups/day versus none was 1.27 (95% CI 1.09 - 1.43), with a highly significant dose-response (p trend = 0.005). No associations were observed with tea consumption. The investigators of this large study concluded that their "findings suggest that high coffee intake during pregnancy may increase risk of childhood ALL."

The researchers further concluded that "current advice to limit caffeine intake during pregnancy to reduce risk of preterm birth may have additional benefits."[36] Thus, this well-designed and well-conducted international study confirms the observation of IARC in its monograph that maternal consumption of coffee during pregnancy increases the risk of childhood leukemia. Incidentally, these findings also contradict OEHHA's statement that coffee "has not been found to increase the risk of any cancers."

Based on the studies regarding the association between maternal consumption of coffee and childhood leukemia, a quantitative estimate of the increased risk of childhood leukemia from maternal coffee drinking during pregnancy was calculated by Dr. Steven P. Bayard, formerly Director of the Office of Risk Assessment in the Directorate of Health Standards Programs within the U.S. Occupational Safety and Health Administration and a quantitative risk assessment expert at the U.S. Environmental Protection Agency and U.S. Consumer Product Safety Commission. Dr. Bayard estimated an increased risk of childhood leukemia from maternal consumption of just 1 cup of coffee per day during pregnancy of 19.5 cases per 100,000 – a substantial risk indeed.[37] Regrettably, in its Monograph on Coffee IARC does not discuss the biological mechanisms that would explain the association between maternal consumption of coffee and childhood leukemia. During the Phase 1 trial in *CERT v. Starbucks,* I explained that "the most probable mechanism to explain [the association] is that the clastogenic chemicals within coffee, including acrylamide, cross into the fetus and cause genetic damage in the fetus of the type where there's chromosome breakage, which leads to chromosome translocations, which then develops into leukemia."[38] [See also Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C, Miller M, Attia J, Scott RJ, Kirby M, Armstrong BK, "Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study," *Cancer Causes Control* (2011) 22:207-218; Sörgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, Landeersdorfer C, "Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans," *Chemother.* (2002) 48(6):267-274; Annola K, Karttunen V, Keski-Rahkonen P, Myllynen P, Segerbäck D, Heinonen S, Vähäkangas K, "Transplacental transfer of acrylamide and glycidamide are comparable to that of antipyrine in perfused human placenta," *Toxicol. Lett.* (2008) 182:50-56].

Four meta-analyses have been published regarding maternal consumption of coffee during pregnancy and childhood leukemia.

The earliest meta-analysis published in 2011, based on three case-control studies, reported a statistically significant greater than 2-fold increased risk of childhood leukemia from maternal consumption of more than 3 cups of coffee per day in nonsmoking mothers (OR 2.32, 95% CI 1.51 - 3.57), with a dose-response relationship. Interestingly, the authors observed no change in risk for equivalent consumption of coffee among smoking mothers (OR 1.01, 95% 0.77 - 1.33), indicating that the greater than doubling of the risk of childhood leukemia from high maternal consumption of coffee during pregnancy is unlikely the result of confounding by smoking.[39]

A meta-analysis published by Chinese investigators in 2014, based on seven case-control studies, also reported an increased risk of childhood leukemia in association with high maternal

coffee consumption (OR 1.72, 95% CI 1.37 - 2.16). Comparing the highest level of consumption with non-lowest consumption of coffee, significantly increased risks wee observed for both childhood acute lymphoblastic leukemia (OR 1.65, 95% CI 1.28 - 2.12) and acute myeloid leukemia (OR 1.58, 95% CI 1.20 - 2.08).[40]

A meta-analysis published in 2015 by Greek researchers, based on eight case-control studies, reported a greater than 50% increased risk of childhood leukemia comparing highest verses never-lowest maternal consumption of coffee during pregnancy (OR 1.57, 95% CI 1.16 - 2.11).[41]

The most recent meta-analysis, published by Chinese researchers after IARC completed its review, reported an increased risk of childhood acute lymphoblastic leukemia in association with maternal consumption of coffee during pregnancy (OR 1.44, 95% CI 1.07 - 1.92).[42]

As IARC noted, the meta-analyses regarding maternal consumption of coffee and childhood leukemia "all reported elevated risks with higher levels of maternal coffee intake" as well as statistically significant increased risks of both major types of childhood leukemia. *Id.* at p. 296.

In my opinion, the evidence of increased risk of childhood leukemia with maternal consumption of coffee during pregnancy is compelling and merits classification at least at the level of *limited evidence of carcinogenicity*, i.e., "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the IARC Monograph Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence." In any case, the epidemiological data certainly do not support the claim by OEHHA that coffee "has not been found to increase the risk of any cancers."

5. Due to its Caffeine Content, Maternal Coffee Consumption Retards Fetal Growth

Coffee contains caffeine, which is clearly a developmental toxicant.[43]

Several meta-analyses over the past two decades have evaluated the risk of low birth weight from maternal consumption of coffee during pregnancy. Fernandez reported a greater than 50% increased risk of low birth weight in children whose mothers consumed 1 strong cup of coffee per day during pregnancy.[44] Santos reported that aggregated results show an average decrease in birth weight of nearly 43 grams among newborns of the heaviest caffeine-consuming mothers.[45] Chen reported that higher caffeine intake during pregnancy was associated with a higher risk of delivering low birth weight infants. In the dose-response analysis, each 100-mg/day increment in maternal caffeine intake (around one cup of coffee) was associated with 13% (RR 1.13, 95% CI 1.06 -1.21) higher risk of low birth weight. The authors concluded that these findings support recommendations to restrict caffeine intake during pregnancy.[46] Greenwood found similarly and concluded that there is no identifiable threshold below which the association is not apparent. Their results confirm the precautionary guidance adopted by countries recommending limiting coffee/ caffeine consumption during pregnancy.[47] Rhee found that the highest versus lowest level of caffeine intake during pregnancy resulted in a 38%

increased risk of low birth weight.[48] These meta-analyses consistently show adverse effects on birth weight at coffee/ caffeine consumption levels below the reputedly safe maximum levels cited by some authorities.

A large prospective, observational study by the CARE study group of 2635 low risk pregnant women showed increased risks of fetal growth restriction for different levels of caffeine consumption. The relation between total caffeine intake in pregnancy and fetal growth restriction showed a significant trend with increasing caffeine intake (test for trend P=0.02⇓). Compared with caffeine intake of <100 mg/day, the odds ratio of having a growth restricted baby increased to 1.2 (95% confidence interval 0.9 to 1.6) for intakes of 100-199 mg/day, to 1.5 (1.1 to 2.1) for intakes of 200-299 mg/day, and to 1.4 (1.0 to 2.0) for intakes of ≥300 mg/day. This relation was consistent across all three trimesters. Students in my Risk Assessment class this past Spring used the EPAs benchmark dose software to analyze this study and showed the safe level of intake for caffeine was less than 50 mg for a pregnant woman in order to prevent retardation of growth of the fetus. This is less than one cup of coffee per day.

The caffeine in coffee is therefore a developmental toxicant as indeed is the heat-formed carcinogen, acrylamide that is also present at significant levels in coffee. A number of studies show that maternal exposure during pregnancy to dietary acrylamide significantly retards fetal growth and decrease birth weight (along with head circumference).[50-52] Since coffee is the largest source of acrylamide in the adult diet, I am able to conclude that maternal consumption of coffee during pregnancy probably retards fetal growth and reduces birthweight of newborns, most likely due to combined effects of caffeine and acrylamide in coffee.

In conclusion, based on the above points, I would strongly recommend OEHHA reconsider their proposed regulation that would declare all listed heat-formed carcinogens in coffee to present no significant risk of cancer. The proposed regulation has no solid scientific foundation.

Sincerely,

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